IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Application of:

Jacques DUMAS et al.		Confirmation No.:	8474
Serial No.:	09/472,232	Examiner:	Deepak Rao
Filed:	December 27, 1999	Group Art Unit:	1624
Title:	INHIBITION OF RAF KINASE USING ARYL AND HETEROARYL SUBSTITUTED HETEROCYCLIC UREAS		

REPLY BRIEF

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Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

Sir:

In response to the Examiner's Answer mailed May 26, 2006, herewith is Appellant's Reply Brief.

The Examiner's Answer does not raise any new issues with regard to the claims on appeal and still fails to provide any evidence to support the rejection under 35 U.S.C. §112, first paragraph. Therefore, the remarks in the Brief on Appeal are adequate in presenting Appellant's position. However, the Examiner's Answer presents the following new point of argument regarding the rejection under 35 U.S.C. §112, first paragraph.

1. The Examiner's Answer includes several statements regarding the state of the art with respect to oncology, for example, page 4, lines 4-5 of the Answer state, "no compound has ever been found to treat cancers of all types generally," lines 6-7 of the Answer state, "The existence of such a "silver bullet" is contrary to our present understanding of oncology" and. lines 13-14 of the Answer state, "Thus, it is beyond the skill of oncologist today to get an agent to be effective against cancers and/or diseases mediated by RAF kinase in general" The Examiner's Answer also states at page 5, lines 1-2, "There are no known compounds of similar structure, which have been demonstrated to treat all types of cancers;" and at page 8, lines 1 and 2, "the state of the art references do not establish a therapeutic method for the treatment of cancerous cell growth mediated by RAF kinase generally." Furthermore, at page 9, lines 3-4 the Answer states, " the art does not identify a single class of compounds that can treat all these types of cancers generally."

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On: July 26 2006
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The Examiner has not provided any evidence to support these statements. While Appellants cannot identify a "silver bullet" which treats all types of cancer, it is recognized that some drugs, once approved for a treatment of a particular disease, are used off label to treat others. For example, carboplatin is approved for the treatment of ovarian cancer but those skilled in the art have recognized it has been used for the treatment of cancer of the bladder, breast, esophagus, fallopian tube, head and neck, testicles, lymph systems, lung, malignant melanoma, tumors of the brain and others. (See, www.nlm.nih.gov/medlineplus/druginfo/uspdi/202115). In addition, reference is made to US Patent Nos. 5,717,100, 5,994,412 (claim 4), 6,486,185 (claim 27), 6,683,082 (claim 16) and 6,861,418 (claim 9) which contain claims to diseases mediated by protein kinases such as raf kinase. Clearly the statements within the Examiner's Answer regarding the state of the art of oncology are inconsistent with the disclosures and claims within these patents and the on-line information from NIH.

Furthermore, Appellant's do not claim treating "all types of cancers" and do not claim the compounds disclosed are "silver bullets." The diseases to be treated are mediated by raf kinase, which is consistent with the activity demonstrated by the assay disclosed in the application. The claims presented are consistent in scope with those found in US Patent Nos. 5,717,100, 5,994,412 (claim 4), 6,486,185 (claim 27), 6,683,082 (claim 16) and 6,861,418 (claim 9). No evidence has been presented that the assay disclosed in the application is ineffective for predicting the pharmaceutical use of the instant compounds and supporting the method of treatment claims.

2. The Examiner's Answer states on page 5, line 10, "There are no doses present to direct one to protect a potential host from the disorders embraced by the instant claims nor there are doses given for the treatment of the disorders recited."

Appellants submit that the disclosure given at page 16, lines 21-29 of the present application provides sufficient guidance to direct one skilled in the art to select dosages for treating the disorders claimed.

3. The Examiner's Answer states on page 6, lines 1 –2, that, "The quantity of experimentation needed would be an undue burden to one skilled in the pharmaceutical arts since there is inadequate guidance given to the skilled artisan, regarding the pharmaceutical use."

In addition to the disclosure within the application mentioned above regarding the dosage of the active compounds, pages 14-16 of the application describe modes and methods of administration such that there is clearly adequate disclosure for one skilled in the art to administer the claimed compounds without undue experimentation.

4. The Examiner's Answer states on page 10, lines 7-10, that, "The specification broadly describes administration procedures and ranges of dosage regimen, however, it is indicated that the method of administration and/or the dose levels depend on the number of factors which have to be evaluated by one of ordinary skill in the art. These factors included a)...b)...c) and d)."

The factors a) – d) reported in the Answer do not appear in the Appellants application. Factors, which Appellants do identify, appear on page 17, lines 2-14, of the application and include, "specific activity of the compound administered, age, body weight, health, sex, diet, time and route of administration, rate of excretion, drug combination and the severity of the condition under going therapy.

5. On page 10, lines 15-16, the Examiner's answer states, "applicant's have not asserted that it is art recognized that the assays are correlated to clinical efficacy for treatment of all types of diseases mediated by RAF kinase."

It is noted that such an assertion is not necessary to satisfy the requirements of 35 U.S.C. 112, first paragraph, and no evidence has been presented that these assays are inadequate, as is required to support the rejection.

6. On page 12, line 11, the Answer indicates that, "Appellants reliance on the *Brana* decision is erroneous since the facts were different in more than one respect form the instant case.

Appellants have not relied on the analysis of the facts in *In re Brana*. Appellants have cited *Brana* for Federal Circuit's analysis of the law regarding the utility requirement and the courts general observation that the "purpose of treating cancer with chemical compounds does not suggest an inherently unbelievable undertaking or involve implausible scientific principles." Therefore, Appellants' reliance on Brana is not erroneous.

7. On page 12, lines 19-20, the Answer states *In re Buting* is on point and more applicable.

The art of oncology has developed significantly since the decision in *In re Buting* and as set forth in *Brana* the "purpose of treating cancer with chemical compounds does not suggest an inherently unbelievable undertaking or involve implausible scientific principles." Therefore, the level of evidence of utility need not be as high as that required in *In re Buting*.

35 U.S.C. §103(a)

The Examiner's Answer presents the following new points of argument regarding the rejection under 35 U.S.C. §103(a).

8. In maintaining the rejection under 35 U.S.C §103, the Examiner has formulated subgenera for use in an obviousness analysis improperly relying on hindsight.

In referring to the disclosure within the reference (Regan et al. U.S. Patent No. 6,080,763) on page 6 of the Answer, the examiner makes the selections necessary for the variables "HET", "Y" and "X. " and the definition of R^5 is abbreviated to conform to the selections necessary to arrive at the compounds claimed herein. The abbreviated definition reads as follows, "R^5 is phenyl, naphthyl, etc. which is further substituted by one to five substituents which substituent list includes alkyl, halo, cyano, phenyloxy, naphthyloxy, phenylamino, naphthylamino, etc."

The actual definition R^5 comprises over 80 lines of text in the patent and encompasses many moieties. The abbreviated definition does not conform to any subgenus disclosed by the reference and, in addition, there is no basis for assuming such a subgenus would apply to

compounds where the values for "HET", "Y" and "X" conform to the compounds claimed herein. Only Appellants application provides the direction necessary to make these selections.

In addition, not one example is given of a compound with a phenyloxy, naphthyloxy, phenylamino or naphthylamino group, so there is no basis to assume they are equivalent to those illustrated by Regan. There are significant structural differences between the groups R_5 actually employed by Regan and those employed by the compounds of the present invention and there is no basis to assume compounds with such structural differences will have the same function.

The Examiner identifies compounds of examples 18 and 34 of Regan et al. and alleges it would be a simple substitution of one substituent to obtain a compound of the present invention. However, by starting with compounds 18 and 34 and ignoring the other examples, the examiner has preselected values for "HET", "Y" and "X" using, in hindsight, Appellants application as a guide. There is no motivation or direction to pair the selections for "HET", "X" and "Y" with the specific selections necessary from the broad definition of R_5 to arrive at compounds of this invention. Put another way, there is no basis to select compounds 18 and 34 from those disclosed by Regan as a subgenus for modification in a manner necessary to arrive at compounds claimed herein.

The Commissioner is hereby authorized to charge any fees associated with this response or credit any overpayment to Deposit Account No. 13-3402

Respectfully submitted,

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